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Clinical and Prognostic Characteristics of Acute BAD–Related Stroke: A Multicenter MRI–Based Prospective Study

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BACKGROUND: Branch atheromatous disease (BAD)–related stroke has emerged as a meaningful subtype of ischemic stroke yet remained understudied. We aimed to investigate the demographic, clinical, therapeutic, and prognostic characteristics of BAD-related stroke.

METHODS: The BAD-study was a nationwide, multicenter, prospective, observational cohort study in 20 Chinese hospitals from June 2021 to June 2023, enrolling patients aged 18 to 80 years with BAD-related stroke within 72 hours of onset. Eligible single subcortical infarct in the territory of lenticulostriate artery and paramedian pontine artery was included. Clinical, laboratory, and treatment data were collected at baseline. The primary outcome was a proportion of good outcomes (modified Rankin Scale score, 0–2) at 90 days. Main secondary outcomes included early neurological deterioration (END), cerebrovascular event, major bleeding, and excellent outcome (modified Rankin Scale score, 0–1) during 90-day follow-up.

RESULTS: We finally enrolled 476 patients, with a median age of 60 (interquartile range, 53–68) years, and 70.2% were male. The median National Institutes of Health Stroke Scale score was 3 (interquartile range, 2–6) at enrollment. Involvement of the lenticulostriate artery was more common than the paramedian pontine artery (60.7% versus 39.3%). END occurred in 14.7% of patients, with a median time from onset of 38 (interquartile range, 22–62) hours. The rates of good and excellent outcomes were 86.5% and 72%, respectively. Its 90-day stroke recurrence rate was 1.9%. Acute-phase therapy (from onset to 7 days of enrollment) showed heterogeneity and was not associated with prognosis. Multivariable logistic regression analysis identified the National Institutes of Health Stroke Scale score ≥4 at admission and END as negative predictors and extracranial artery stenosis as a positive predictor of good outcomes. Age ≥60 years, National Institutes of Health Stroke Scale score ≥4 at admission, and END were negative predictors of excellent outcomes.

CONCLUSIONS: With distinct demographic, clinical, and prognostic characteristics, along with a high incidence of END and a low risk of stroke recurrence, BAD-related stroke could be categorized as a separate disease entity. Moreover, its acute-phase treatment strategies were undetermined, awaiting further high-quality studies.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arterial occlusive diseases ■ atherosclerosis ■ constriction, pathologic ■ neuroimaging ■ prognosis ■ stroke

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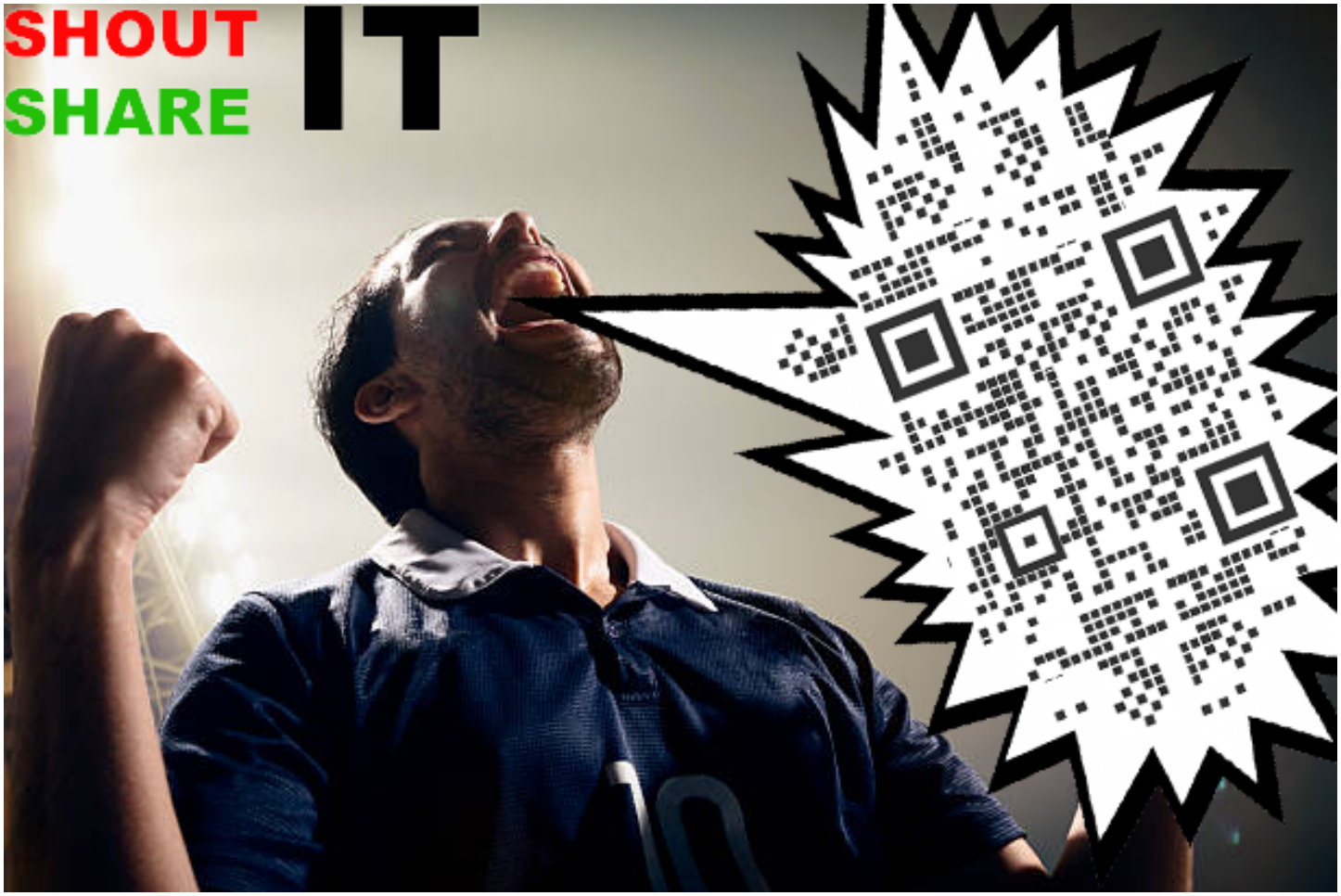
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Nonstandard Abbreviations and Acronyms

BAD	branch atheromatous disease
END	early neurological deterioration
IQR	interquartile range
LSA	lenticulostriate artery
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PPA	paramedian pontine artery
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

Branch atheromatous disease (BAD), first described in 1989 by Caplan,[1] was characterized by stenosis or occlusion at the origin of a penetrating artery, leading to subcortical infarction. Unlike lacunar infarcts resulting from lipohyalinotic degeneration, BAD was attributed to atherosclerosis.[2] Due to a lack of further pathological studies, BAD remained a neglected and underused concept for decades. With the aid of magnetic resonance imaging (MRI), recent studies found that BAD-related stroke was more common in the Asian population, prone to early neurological deterioration (END), and associated with poor outcomes.[3–5] BAD-related stroke is increasingly becoming a clinical entity.

Nevertheless, the classification of BAD-related stroke within the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) system has been limited, with most cases categorized under small vessel occlusion or undetermined cause. For example, 12.6% of undetermined causes of stroke could be diagnosed with BAD.[6] Consequently, acute BAD–related stroke has received scant attention in research endeavors, compounded by variations in diagnostic criteria, data collection, and outcomes across previous studies.[4,7,8] As such, there exists a critical gap in scientific knowledge about BAD-related stroke.

Several imaging features supported the atherosclerotic mechanisms of BAD. For lenticulostriate artery (LSA) territory, lesions involving ≥4 consecutive slides in the axial plane were in favor of atherosclerosis; for paramedian pontine artery (PPA) territory, lesions affecting the ventral pontine were.[2,9] With reference to clinical practice and vascular mechanisms, we proposed imaging criteria for the diagnosis of BAD, which was distinct from cerebral small vessel disease and large-artery atherosclerotic stroke.[10,11]

To address the scientific gap, we conducted the BAD-study, a multicenter prospective cohort study in China, to investigate the demographic, clinical, treatment, and prognostic characteristics of BAD-related stroke.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We report our study according to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).

Study Design and Participants

Detailed information about the BAD-study design and participant recruitment has been outlined elsewhere.[11] In brief, the BAD-study was a nationwide, multicenter, prospective, observational cohort study covering 20 Chinese hospitals between June 2021 and June 2023. Only patients aged 18 to 80 years with BAD-related stroke within 72 hours after onset and meeting all the following radiological criteria were enrolled: (1) diffusion-weighted imaging lesion: single (isolated) deep (subcortical) infarct; (2) the culprit vessels were LSA or PPA, and the infarct lesion on diffusion-weighted imaging conformed to one of the following characteristics (A/B): (A) LSA: comma-like infarct lesions with fan-shaped extension from bottom to top in the coronal plane or ≥3 layers (layer thickness, 5–7 mm) on axial diffusion-weighted imaging and (B) PPA: the infarct lesion extended from the deep pons to the ventral pons on the axial diffusion-weighted imaging; and (3) no ≥50% stenosis on the parent artery of the criminal vessel. The main exclusion criteria included: (1) intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain abscesses, malignant space-occupying lesions, or other nonischemic intracranial lesions at baseline; (2) ≥50% stenosis of extracranial vessels with ipsilateral serial relationship; (3) cardiogenic embolism; and (4) stroke caused by other clear causes. Before enrollment, patients underwent brain MRI and intracranial and extracranial vascular examination to confirm radiological criteria for BAD-related stroke, especially distinguishing it from cerebral small vessel disease (Table S1). The BAD-study was approved by the Peking Union Medical College Hospital (No. ZS-2982B), and all patients provided written informed consent.

Clinical Data Collection and Outcome Assessment

Data on demographics, medical history, clinical presentation, National Institutes of Health Stroke Scale (NIHSS) scores, modified Rankin Scale (mRS) scores, Barthel Index scores, treatments, and laboratory parameters were prospectively collected at baseline. The acute phase indicated time from onset to 7 days of enrollment.

In addition, the stenosis of intracranial and extracranial arteries was recorded. Subsequent follow-up data at 7, 30, and 90 days were obtained locally and reviewed centrally.

The primary outcome was a good outcome, defined as mRS 0 to 2 at 90 days with single-blinded evaluation. Secondary outcomes include END within 7 days, Barthel index, new vascular events (myocardial infarction, new-onset ischemic stroke, and new-onset intracranial hemorrhage), and major bleeding during 90-day follow-up. Excellent outcome defined as mRS 0 to 1 at 90 days was also listed as a secondary outcome. In addition, major bleeding and END events were judged according to the definitions and documented in detail.[11,12]

The END was defined as follows: (1) from symptom onset to 7 days after enrollment and (2) Occurrence of deterioration of neurological deficits after initial assessment: an increase of

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the NIHSS score ≥4 points or NIHSS motor score ≥1 point for ischemic stroke patients or the stereotyped attacks still repeat ≥3× after arrival at hospital or progress to persistence status for patients with internal capsule warning syndrome or pontine warning syndrome. The time from onset to END was measured as hours.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables with nonnormal distributions were summarized as median (interquartile range). The Pearson χ^2 or Fisher exact test and Wilcoxon tests were used for the statistical significance analysis of the outcomes, where appropriate. The Cox proportional hazards model was used to explore the factors associated with END, where NIHSS score at admission was grouped by 6.[13,14] Multivariable logistic regression was conducted to define independent predictors of good and excellent outcomes, respectively. Odds ratios (ORs) and hazard ratios with 95% CIs were presented. The missing data were deleted from the analysis. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), and 2-sided $P<0.05$ was considered significant.

RESULTS

Demographic and Clinical Characteristics

Of 502 patients with BAD-related stroke within 72 hours of onset, 26 were excluded based on age, MRI examination, and other criteria, resulting in a final cohort of 476 eligible patients. Moreover, 475 patients finished 90-day follow-up, and 1 patient dropped out (Figure S1). The median age was 60 (interquartile range [IQR], 53–68) years, with 14.7% of patients aged <50 years. The male-to-female ratio was nearly 2:1. As for symptoms of BAD-related stroke, 87.6% occurred with a known onset time, only 2.3% were transient ischemic attacks, and 50% showed pure motor symptoms. The median NIHSS score was 4 at admission and 3 at enrollment; 137 (28.8%) patients had an NIHSS score ≥6 at admission (Table S2). At enrollment, the median mRS score and the Barthel index score were 2 and 80, respectively (Table 1). The median hours from onset to admission and enrollment were 15 (IQR, 6–24) and 49 (IQR, 40–64).

Vascular risk factors are also shown in Table 1; 257 (54%) had hypertension, 115 (24.2%) had diabetes, and 85 (17.9%) had a history of stroke; 40.8% were smokers, 25.4% were regular drinkers, and 9.9% had a sedentary lifestyle; 14.6% was obesity; and 9.3% took antiplatelet agent 1 month before onset (Table 1; Table S2).

Laboratory and Radiological Features

Two types of BAD-related stroke were enrolled in the BAD-study, which are shown in the Figure. The numbers of involved LSA and PPA were 289 (60.7%) and 187 (39.3%), respectively. The ratio of LSA to PPA was 3:2. The stenosis rates of intracranial and extracranial

Table 1. Demographic and Clinical Characteristics of Branch Atheromatous Disease–Related Stroke at Baseline

	Total (N=476)
Demographics	
Age at onset, y	60 (53–68)
≤49	70 (14.7)
50–69	320 (67.2)
≥70	86 (18.1)
Sex, male	334 (70.2)
Clinical features	
Onset time	
Clear	417 (87.6)
Wake-up	40 (8.4)
Unknown	19 (4.0)
Type of onset	
Ischemic stroke	465 (97.7)
Transient ischemic attack	11 (2.3)
Type of symptom	
Pure motor symptoms	238 (50.0)
Pure sensory symptoms	10 (2.1)
Motor sensory symptoms	137 (28.8)
Other symptoms	91 (19.1)
NIHSS score at admission	4 (2–6)
NIHSS score at enrollment	3 (2–6)
mRS score at enrollment*	2 (1–3)
Barthel index score at enrollment†	80 (60–100)
SBP ≥160 mm Hg at enrollment‡	85 (17.9)
DBP ≥100 mm Hg at enrollment§	57 (12.0)
Vascular risk factors	
Hypertension	257 (54.0)
Diabetes	115 (24.2)
Elevated LDL-C (self-report)	8 (1.7)
History of IS or transient ischemic attack	77 (16.2)
History of HS	8 (1.7)
History of stroke	85 (17.9)
Coronary heart disease	31 (6.5)
Obesity‖	69 (14.6)
Smoking, ever	194 (40.8)
Regular drinking	121 (25.4)
Sedentary lifestyle	47 (9.9)
Family history of cardiovascular disease¶	61 (12.8)
Criminal artery of ischemic lesion	
Lenticulostriate artery	289 (60.7)
Paramedian pontine artery	187 (39.3)
Stenosis of intracranial artery	175 (36.8)
Stenosis of extracranial carotid artery#	120 (25.2)
Time from onset to admission, h	15 (6–24)
Time from onset to enrollment, h	49 (40–64)

Continuous variables with nonnormal distribution are presented as median (interquartile range); other values are shown as n (%). DBP indicates diastolic blood pressure; HS, hemorrhagic stroke; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

*Missing data: 12.

†Missing data: 72.

‡Missing data: 1.

§Missing data: 1.

‖Obesity was defined as body mass index ≥28 kg/m^2. Missing data: 2.

¶Family history of cardiovascular disease did not include hypertension in our study.

#Extracranial carotid artery includes subclavian artery, vertebral artery, common carotid artery, and internal carotid artery.

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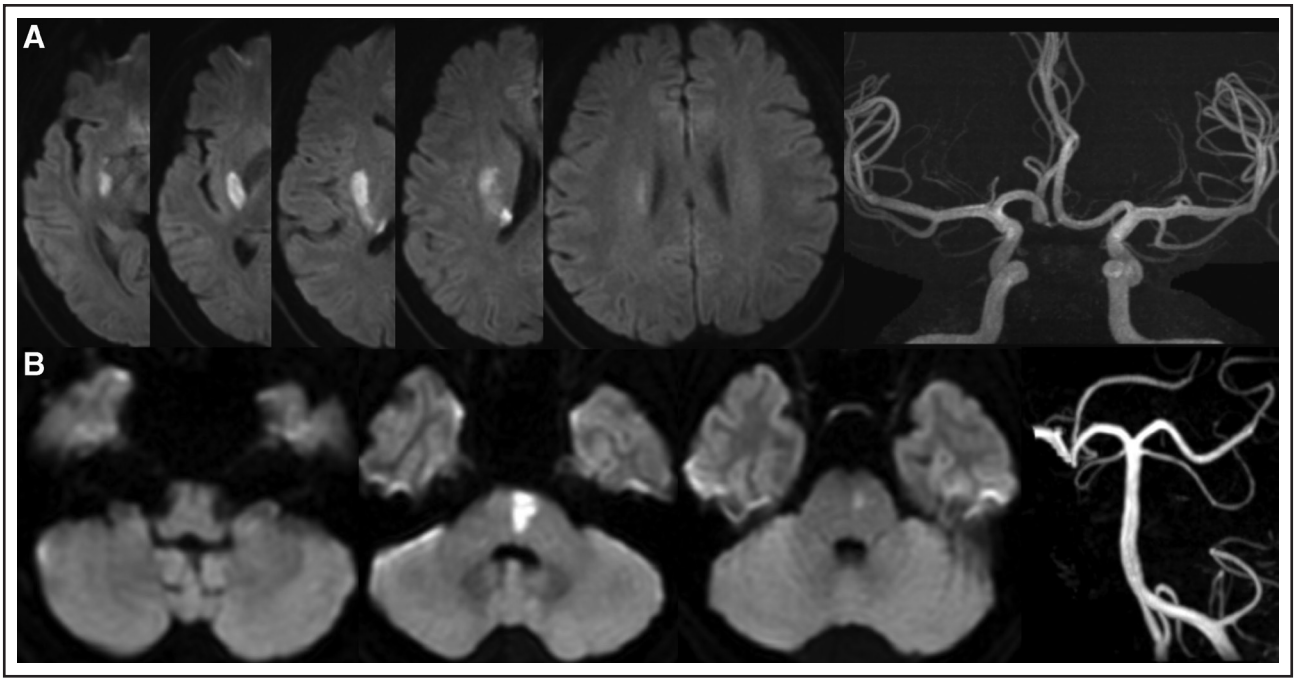

Figure. Neuroimages of single subcortical infarction.
Neuroimages of single subcortical infarction in the territory of (**A**) lenticulostriate artery and (**B**) paramedian pontine artery.

arteries were 36.8% and 25.2%, respectively (Table 1). The laboratory data in detail are shown in Table S2. The baseline rates of increased fasting glucose, hyperhomocysteinemia, and elevated low-density lipoprotein cholesterol levels were 32.4%, 39.2%, and 23.2%, respectively.

Current Treatment for BAD-Related Stroke

At baseline, 74 (15.6%) patients received intravenous thrombolysis, while 85 (17.9%) received anticoagulation therapy. The rate of dual antiplatelet therapy was lower in patients with NIHSS score ≥4 (57.7%) than in those with NIHSS score ≤3 (70.9%) with *P*=0.0108. At 7 days, 52 (11%) patients were still receiving anticoagulation treatment. Fewer patients used statins in those with NIHSS ≥4 than those with NIHSS ≤3 (93.7% versus 97.5%; *P*=0.0478). The rates of intravenous tirofiban were comparable between those with NIHSS score ≥4 and NIHSS score ≤3 (Table 2).

Clinical Outcome and Risk Factors

During the 90-day follow-up period, the rate of good outcomes was 86.5%, and the rate of excellent outcomes was 72% (Table 3; Table S3). The 90-day median mRS score was 1 (IQR, 0–2), and the Barthel index score was 100 (IQR, 90–100). Seventy (14.7%) patients suffered from END, with a median time from onset of 38 hours. Ten patients (2.1%) suffered from new vascular events, and 9 (1.9%) patients had recurrent strokes. In addition, the rate of major bleeding is 0.4%, and nobody died in our BAD-study.

Two Cox regression models in Table 4 present the factors associated with END. NIHSS ≥6 at admission significantly increased the risk of END (19.7% versus 12.7%; hazard ratio, 1.65 [95% CI, 1.01–2.70]; *P*=0.0445). The rate of NIHSS ≥6 at admission tended to be higher in patients receiving tirofiban (36.4% versus 27.4%; *P*=0.1115; Table S4). However, tirofiban was not associated with the occurrence of END. In addition, stenosis of the intracranial artery was associated with a lower risk of END (hazard ratio, 0.34 [95% CI, 0.18–0.64]; *P*=0.0008).

Table 5 shows the risk factors associated with good and excellent outcomes. The probability of a good outcome was low if patients suffered from END (OR, 0.13 [95% CI, 0.07–0.26]; *P*<0.0001) and had an NIHSS ≥4 at admission (OR, 0.27 [95% CI, 0.14–0.52]; *P*=0.0001). Stenosis of the extracranial artery was associated with a good prognosis (OR, 2.88 [95% CI, 1.30–6.37]; *P*=0.0089). As for prediction of excellent outcome, only age ≥60 years (OR, 0.57 [95% CI, 0.35–0.92]; *P*=0.0212), NIHSS ≥4 at admission (OR, 0.23 [95% CI, 0.14–0.39]; *P*<0.0001), and END (OR, 0.16 [95% CI, 0.08–0.30]; *P*<0.0001) showed a significant negative correlation. In addition, no acute-phase therapy could predict the prognosis of BAD-related stroke.

DISCUSSION

BAD-study is the first nationwide large-sample multicenter prospective cohort study, which enrolled patients with acute BAD–related stroke under uniform criteria of enrollment. Prior research has highlighted considerable heterogeneity in defining BAD, raising questions about its status as a separate disease entity.[3,4,7] Our study, characterized

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Table 2. Acute-Phase Therapy of Branch Atheromatous Disease–Related Stroke

	Total (N=476)	Stroke severity at admission		
		NIHSS ≤3 (n=237)	NIHSS ≥4 (n=239)	*P* value
Baseline				
Intravenous thrombolysis	74 (15.6)	32 (13.5)	42 (17.6)	0.2203
Antiplatelet therapy				0.0108
None	34 (7.1)	13 (5.5)	21 (8.8)	
Mono antiplatelet therapy	136 (28.6)	56 (23.6)	80 (33.5)	
Dual antiplatelet therapy	306 (64.3)	168 (70.9)	138 (57.7)	
Anticoagulation therapy	85 (17.9)	35 (14.8)	50 (20.9)	0.0797
Use of statins	445 (93.5)	227 (95.8)	218 (91.2)	0.0435
Day 7 after enrollment				
Antiplatelet therapy*				0.0615
None	7 (1.5)	2 (0.9)	5 (2.1)	
Mono antiplatelet therapy	151 (31.8)	65 (27.5)	86 (36.0)	
Dual antiplatelet therapy	317 (66.7)	169 (71.6)	148 (61.9)	
Anticoagulation therapy†	52 (11.0)	21 (8.9)	31 (13.0)	0.1552
Use of statins‡	454 (95.6)	230 (97.5)	224 (93.7)	0.0478
Use of intravenous tirofiban§	77 (16.2)	33 (14.0)	44 (18.4)	0.1906

Continuous variables with nonnormal distribution are presented as median (interquartile range); other values are shown as n (%).

*Missing data:1.

†Missing data: 1.

‡Missing data: 1.

§It indicates the use of intravenous tirofiban from stroke onset to 7 days after enrollment; missing data: 1.

Table 3. Clinical Outcomes of Branch Atheromatous Disease–Related Stroke at 90 Days

	Total (N=475)
Good outcome	411 (86.5)
Excellent outcome	342 (72.0)
mRS score	1 (0–2)
Barthel index score*	100 (90–100)
≤60	31 (6.5)
≥61	443 (93.5)
END	70 (14.7)
Hours from onset to END	38 (22–62)
Vascular events	10 (2.1)
Stroke	9 (1.9)
Ischemic stroke	7 (1.5)
Myocardial infarction	1 (0.2)
Death	0 (0)
Major bleeding	2 (0.4)
Intracranial hemorrhage	2 (0.4)
Bleeding	6 (1.3)

A good outcome was defined as an mRS score of 0–2. Excellent outcome was defined as an mRS score of 0–1. Continuous variables with nonnormal distribution are presented as median (interquartile range); other values are shown as n (%). END indicates early neurological deterioration; and mRS, modified Rankin Scale.

*Missing data: 1.

by widely accepted enrollment criteria and comprehensive preenrollment MRI evaluation, enhances the representativeness of our findings.[1,10] Bang[15] and Kim and Kim[16] have found a higher prevalence of atherosclerosis in Asian stroke and called for new research into stroke mechanisms. Therefore, the clinical and prognostic outcomes of our investigation promise to offer novel perspectives on ischemic stroke causes within Asian demographics.

The median age of our cohort, 60 years, aligned with previous reports indicating that the mean age of patients with BAD typically ranged from 62 to 69 years, presenting a notable contrast with patients afflicted by cerebral small vessel disease, who tended to be older by 2 to 4 years.[3,4,17–19] The detection rate of cerebral white matter lesions increases with age, which may suggest small vessel disease, whereas we found that <20% of patients with BAD were over 70 years of age and BAD was not more prevalent in the older age groups.[20] Furthermore, we noticed that approximately one-sixth of the patients with BAD-related stroke were <50 years of age, and BAD might be an important cause of ischemic stroke in young adults, which is not currently on the radar of clinicians.[21] Another feature of BAD-related stroke was its prevalence in men, which was consistent with the findings from other studies.[4,22,23]

We found that the median NIHSS score at admission was 4, which was similar to previous studies on BAD[3–5] and was higher than minor stroke (4 versus 2).[24] In contrast to minor stroke studies such as CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke), patients with BAD-related stroke rarely presented as transient ischemic attacks (2.3% versus 27.9%–43.2%).[24,25] Moreover, motor symptoms dominated the clinical presentation of BAD-related stroke, distinguishing it from cerebral small vessel disease.[19] Approximately one-third of our patients presented with NIHSS scores ≥6 at admission, necessitating differentiation from large-artery atherosclerotic disease and emphasizing the importance of prompt intracranial and extracranial vascular assessment.

The vascular risk factors in our study indicated the atherosclerotic mechanism of BAD-related stroke.[1,2] The prevalence of hypertension (54% versus 80.2%–92%) and diabetes (24.2% versus 28.8%–36%) was slightly lower than that in other studies on BAD, probably due to younger population in our study (60 versus 60–69 years).[3,4,8,17] Our findings highlighted hyperhomocysteinemia and elevated low-density lipoprotein cholesterol levels as important risk factors for BAD-related stroke. In addition, the history of stroke in our study was consistent with previous studies on BAD (17.9% versus

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Table 4. Cox Regression Model for Early Neurological Deterioration in Patients With Branch Atheromatous Disease–Related Stroke

	Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥60 y	0.98 (0.60–1.60)	0.9441	1.05 (0.63–1.74)	0.8489
Female sex	1.26 (0.76–2.11)	0.3683	1.14 (0.66–1.96)	0.6387
Hypertension	0.76 (0.46–1.24)	0.2735	0.92 (0.55–1.54)	0.7538
Diabetes	1.01 (0.57–1.78)	0.9688	1.09 (0.60–1.96)	0.7773
SBP ≥160 mm Hg at admission	1.18 (0.72–1.94)	0.5063	1.18 (0.70–1.99)	0.5325
NIHSS ≥6 at admission	1.65 (1.01–2.70)	0.0445	1.81 (1.08–3.05)	0.0251
PPA territory	1.22 (0.74–2.02)	0.4296	1.42 (0.84–2.41)	0.1893
Use of intravenous tirofiban*	1.35 (0.70–2.58)	0.3731	1.12 (0.56–2.25)	0.7449
Homocysteine ≥15.0 μmol/L	…	…	0.63 (0.35–1.12)	0.1161
Stenosis of intracranial artery	…	…	0.34 (0.18–0.64)	0.0008
Stenosis of extracranial artery†	…	…	0.74 (0.39–1.39)	0.3451

Four hundred and seventy-four patients were included in model 1; 421 patients were included in model 2. END indicates early neurological deterioration; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; PPA, paramedian pontine artery; and SBP, systolic blood pressure.

*Nineteen patients received intravenous tirofiban after END and were classed as those without tirofiban.

†Extracranial artery included subclavian artery, vertebral artery, common carotid artery, and internal carotid artery.

13.9%–20%), which was similar to that in patients with large-artery disease (9.4%–23%) and lower than that in patients with cerebral small vessel disease (20%–25.5%).[3,4,26] Zhang et al[3] also reported a lower rate of previous stroke in the BAD-related stroke cohort, in comparison with the cerebral small vessel disease cohort (13.9% versus 31.3%).

Previous studies reported that the proportions of 90-day good and excellent outcomes in patients with large-artery disease treated with endovascular therapy were 46% and 26.9%, respectively.[14] In patients with cerebral small vessel disease, the proportions of long-term good and excellent outcomes were 53%–90.2% and 73.4%.[2–4] The prognosis of our BAD-study was intermediate between cerebral small vessel disease and large atherosclerotic stroke. The long-term prognosis of BAD-related stroke reported in previous studies was inconsistent, probably due to different BAD enrollment criteria. For example, the rate of

Table 5. Multivariable Logistic Regression for Relative Factors Associated With 90-Day Clinical Outcome

	Good outcome		Excellent outcome	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age ≥60 y	0.58 (0.31–1.08)	0.0866	0.57 (0.35–0.92)	0.0212
Male sex	1.01 (0.50–2.03)	0.9770	0.99 (0.55–1.78)	0.9839
Hypertension	…	…	0.98 (0.61–1.59)	0.9475
Diabetes	…	…	0.66 (0.38–1.13)	0.1275
Coronary heart disease	…	…	0.64 (0.26–1.55)	0.3200
History of stroke	0.62 (0.30–1.26)	0.1826	0.81 (0.45–1.46)	0.4830
Smoking, ever	1.96 (0.95–4.06)	0.0683	1.09 (0.63–1.88)	0.7680
NIHSS ≥4 at admission	0.27 (0.14–0.52)	0.0001	0.23 (0.14–0.39)	<0.0001
END	0.13 (0.07–0.26)	<0.0001	0.16 (0.08–0.30)	<0.0001
Intravenous thrombolysis	1.84 (0.76–4.45)	0.1783	1.76 (0.88–3.52)	0.1074
Dual antiplatelet therapy	1.16 (0.64–2.13)	0.6242	1.54 (0.95–2.48)	0.0782
Use of intravenous tirofiban	…	…	0.83 (0.45–1.54)	0.5591
PPA territory	1.39 (0.75–2.58)	0.2943	1.44 (0.88–2.35)	0.1501
Stenosis of intracranial artery	1.12 (0.58–2.15)	0.7334	0.93 (0.57–1.52)	0.7651
Stenosis of extracranial artery*	2.88 (1.30–6.37)	0.0089	1.70 (0.97–2.96)	0.0635

A good outcome was defined as an mRS score of 0 to 2; an excellent outcome was defined as an mRS score of 0 to 1. END indicates early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PPA, paramedian pontine artery.

*Extracranial artery included subclavian artery, vertebral artery, common carotid artery, and internal carotid artery.

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90-day mRS 0 to 1 ranged from 20% to 56%. Kwan et al[4] included patients with high-grade intracranial stenosis as BAD, where its rate of mRS score 0 to 2 was 39%. Thus, our large-sample prospective cohort further clarified the long-term prognosis of BAD-related stroke. When we considered the high proportion of mRS score ≥2 (28%) and Barthel index score ≤60 (6.5%), BAD-related stroke left a substantial and unignorable percentage of functional disability. Moreover, different from the high stroke recurrence rate of interest in the CHANCE or POINT studies, the rate of stroke recurrence in patients with BAD-related stroke was remarkably low, with a 90-day stroke recurrence rate of 1.9% in our cohort and an annual stroke recurrence rate of no more than 3.8% in another Chinese cohort.[3] Thus, acute-phase therapy is supposed to focus on how to reduce the incidence of END and improve their 90-day functional prognosis, rather than on how to reduce the stroke recurrence rate in patients with BAD-related stroke.

Another prominent feature of BAD-related stroke is the high incidence of END. Our study found that the incidence of END was 14.7%, which was comparable to that observed in patients with large-artery disease (15.8%).[27] We further clarified the occurrence time of END, which will assist clinicians in developing a time window of intervention. Notably, END substantially diminished the likelihood of achieving good and excellent outcomes. Duan et al[28] also found that the rates of mRS score 0 to 2 were 84.6% and 58.4% in those without and with END. In the multivariable analysis for prognosis, only age, NIHSS score at admission, and END were found to be statistically significant. Although Men et al[17] suggested the association between homocysteine and the prognosis of BAD-related stroke, our study did not find other clinical, laboratory, or radiological characteristics to be linked to the 90-day clinical outcome.

Previous studies reported that female sex, high NIHSS score, pontine lesion, and hyperhomocysteinemia predicted END.[13,17] Our study confirmed that an NIHSS score ≥6 predicted END, which might indicate more aggressive treatment at the acute phase of BAD-related stroke. A Chinese randomized control trial reported that tirofiban significantly reduced the rate of END from 13.2% to 4.2% in patients with noncardioembolic stroke, but our results were negative.[29] As an observational study, our risk factors of END should be interpreted with caution. Currently, how to predict the END of BAD-related stroke still remains a major challenge for neurologists, warranting further research.

Our diagnosis of BAD was based on conventional MRI and clinical features. Further introduction of vessel wall imaging might elucidate END mechanisms and predict prognosis, for example, identifying the plaque occluding the orifice of the perforating artery and differing the subtypes of BAD proposed by Caplan.[1,30]

Researchers have explored the effect of several regimens in the acute phase of BAD-related stroke, including dual antiplatelet therapy, tirofiban, anticoagulation therapy, intravenous thrombolysis, etc, but results were controversial and no drugs were recommended to date.[22,31–34] Our study found significant treatment heterogeneity in the acute phase, and unfortunately, in multivariable analysis, all current treatments in clinical practice failed to improve the prognosis of BAD-related stroke. This treatment dilemma necessitates further investigation through high-quality studies.

Our study had several limitations. First, perforating arteries involve LSA, PPA, Heubner artery, etc, but our study only enrolled those with ischemic stroke in territories of PPA and LSA, and patients with >72 hours from the onset were excluded, which might generate selection bias. Second, patients with severe stenosis or occlusion of the parent artery or atrial fibrillation were not considered to have a BAD mechanism, but some researchers have categorized them as such.[4] Third, we only included patients with BAD-related stroke and were unable to compare them with strokes of other etiologies in the TOAST system. Future comparative studies of different groups would be worthwhile. Finally, the number of outcome events in the multivariable analysis was small, and some results required further large-sample studies to analyze the cause. For example, stenosis of the extracranial arteries might increase the proportion of good outcomes, but its underlying reason was unclear.

CONCLUSIONS

Our study demonstrated that BAD-related stroke was not only a clinical concept, but, with the aid of neuroimaging, it could be categorized as a separate disease entity, with distinct demographic, clinical, and prognostic characteristics, high incidence of END, and low risk of stroke recurrence. Moreover, its acute-phase treatment strategies were heterogeneous and ineffective, awaiting further high-quality studies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figure S1

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